REMARKS/ARGUMENTS

The Status of the Claims.

Claims 1-15 and 73-93 are pending with entry of this amendment, dependent claims 4 and 73-76 being withdrawn from consideration until the generic claim is found to be allowable. Claims 1, 92 and 93 are amended herein. These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

Claims 1, 75, 92 and 93 have been amended to address informalities and further clarify the invention, as helpfully suggested by the Examiner. Applicants submit that no new matter has been added to the application by way of the above Amendment. Accordingly, entry of the Amendment is respectfully requested.

Telephonic conference

Applicants respectfully thank Examiner Lucas and Examiner Housel for the suggestions made in the telephonic interview held August 31, 2005.

The Information Disclosure Statement.

Applicants note with appreciation the Examiner's thorough consideration of the Matzku reference initially cited in the Information Disclosure Statement (Form 1449) submitted on July 7, 2003.

35 U.S.C. §112, Second Paragraph.

Claims 92 and 93 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite with respect to the terms "member cell" and "said cell." Applicants have amended the claims to address these informalities and respectfully request that the rejections be withdrawn.

35 U.S.C. §103(a)

The claims are patentable over Hein, Hurwitz and Rakowitz-Szulczynska

The rejection of claims 1, 3, 5, 10, 13-15 under 35 U.S.C. §103(a) as allegedly unpatentable over Hein et al. in light of Hurwitz et al. and Rakowicz-Szulczynska was maintained and extended to include claims 77, 78, 81, 83-85, 87-89, 92 and 93. Applicants traverse in light of the amended claims and respectfully request that the rejection be withdrawn.

As noted previously, three requirements must be met for a *prima facie* case of obviousness. First, the prior art reference must teach all of the limitations of the claims (MPEP § 2143.03). Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention (MPEP § 2143.01). Third, a reasonable expectation of success is required (MPEP § 2143.02). The teaching or suggestion to combine and the expectation of success must be both found in the prior art and not based on Applicants' disclosure (MPEP §2143).

Applicants submit that the cited art does not teach or describe the methods of the claimed invention. Claim 1 as amended is drawn to methods of detecting ligand internalization into a cell, including the step of dissociating the reporter from non-internalized ligand bound to the cell surface and removing dissociated reporter from the surface of said cell while the non-internalized ligand remains bound to the cell surface. As noted by the Office, Hein does not teach the step of dissociating reporter from ligand and removing dissociated reporter from the surface of said cell. Hurwitz and Rakowicz-Szulczynska are alleged to teach methods using a second labeled antibody as a reporter for detecting primary antibody binding, during which the buffer used to remove non-internalized Mab from the cell surface would potentially dissociate the labeled second antibody (reporter) from the primary antibody (ligand). However, the cited references do not teach or describe removing the dissociated reporter from the cell surface while the non-internalized ligand remains on the cell surface. Since the cited references, either alone or in combination, do not teach all of the limitations of the claimed invention, the first criteria for *prima facie* obviousness has not been met. Applicants respectfully request that the rejection be withdrawn.

CLAIMS 2 AND 8 ARE PATENTABLE OVER HEIN, HURWITZ, RAKOWITZ-SZULCZYNSKA, BURMER, COLLINS AND FREED

The rejection of claims 2 and 8 under 35 U.S.C. §103(a) as allegedly obvious in light of Hein et al. in view of Hurwitz et al. and Rakowitz-Szulczynska et al., and in further view of Burmer et al (USPN 6,087,103) and Collins (USPN 5,770,422) and Freed (USPN 5,597,719) was maintained and extended to claims 79 and 86. Applicants traverse in light of the amended claims and respectfully request that the rejection be withdrawn.

Claims 2 and 8 is drawn to methods for detecting ligand internalization employing epitope tags, claim 79 is drawn to methods as performed in a microtiter plate, and claim 86 involves contacting the cell with at least two ligands. Since these claims are dependent from claim 1, the methods include the step of dissociating the reporter from non-internalized ligand bound to the cell surface and removing dissociated reporter from the surface of said cell while the non-internalized ligand remains bound to the cell surface. As noted above, neither Hein nor Hurwitz nor Rakowitz-

Szulczynska teach or describe methods in which the dissociated reporter is removed from the cell surface while the ligand remains bound to the cell surface. Burmer does not remedy this deficit; there is no mention of removing a reporter from a ligand after binding of the ligand to a target. Rather, the continued association of the reporter with the ligand appears to be necessary in order to provide the "known address" needed for identification purposes during the detecting step. Collins and Freed, which are directed toward using epitope tags as labels, also do not teach or describe removing dissociated reporter, but not ligand, from the surface of said cell. Since the cited references, either alone or in combination, do not teach all of the limitations of the claimed invention, the first criteria for *prima facie* obviousness has not been met. Applicants respectfully request that the rejection be withdrawn.

CLAIMS 6 AND 7 ARE PATENTABLE OVER HEIN, HURWITZ, AND RAKOWITZ-SZULCZYNSKA IN FURTHER VIEW OF BARBAS AND WARD

The rejection of claims 6 and 7 under 35 U.S.C. §103(a) as allegedly obvious in light of Hein et al. in view of Hurwitz et al. and Rakowitz-Szulczynska et al., and in further view of Barbas et al. (Proc. Acad. Natl. Sci. USA 88:7978-7982) and Ward et al. (J. Immunol. Methods 189:73-82) was maintained. Applicants traverse in light of the amended claims and respectfully request that the rejection be withdrawn.

Claims 6 and 7 are drawn to methods for detecting ligand internalization involving ligands from combinatorial libraries. Since these claims are dependent from claim 1, the methods include the step of dissociating the reporter from non-internalized ligand (i.e., combinatorial library member) bound to the cell surface and removing dissociated reporter from the surface of said cell while the non-internalized ligand remains bound to the cell surface. As noted above, neither Hein nor Hurwitz nor Rakowitz-Szulczynska teach or describe methods in which the dissociated reporter, but not the ligand, is removed from the cell surface. Barbas and Ward do not remedy this deficit. The Barbas publication relates to the production of phage display libraries; the Ward publication describes the isolation of antibodies from libraries through the use of an enzymatic cleavage site. Neither reference teaches or describes methods in which the dissociated reporter is removed from the cell surface while the ligand remains bound to the cell surface. Since the cited references, either alone or in combination, do not teach all of the limitations of the claimed invention, the first criteria for *prima facie* obviousness has not been met. Applicants respectfully request that the rejection be withdrawn.

CLAIMS 9-11 ARE PATENTABLE OVER HEIN, HURWITZ, AND RAKOWITZ-SZULCZYNSKA IN FURTHER VIEW OF PLANT AND SZOKA

The rejection of claims 9-11 under 35 U.S.C. §103(a) as allegedly obvious in light of Hein et al. in view of Hurwitz et al. and Rakowitz-Szulczynska et al., and in further view of Plant et al. (USPN 5,389,523) and Szoka et al. (USPN 6,593,308) was maintained. Applicants traverse in light of the amended claims and respectfully request that the rejection be withdrawn.

Claims 9-11 are drawn to methods for detecting ligand internalization involving epitope tags and/or various reporters. Since these claims are ultimately dependent from claim 1, the methods also include the step of dissociating the reporter from non-internalized ligand bound to the cell surface and removing dissociated reporter from the surface of said cell while the non-internalized ligand remains bound to the cell surface. As noted above, neither Hein nor Hurwitz nor Rakowitz-Szulczynska teach or describe methods in which the dissociated reporter is removed from the cell surface while the ligand remains bound to the cell surface. Plant and Szoka do not remedy this deficit; Plant discusses detection of peptides coupled to liposomes, while Szoka is alleged to teach drug delivery compositions involving liposomes. Neither publication teaches or describes methods in which a dissociated reporter, but not the ligand, is removed from a cell surface. Since the cited references, either alone or in combination, do not teach all of the limitations of the claimed invention, the first criteria for *prima facie* obviousness has not been met. Applicants respectfully request that the rejection be withdrawn.

CLAIMS 9 AND 12 ARE PATENTABLE OVER HEIN, HURWITZ, AND RAKOWITZ-SZULCZYNSKA IN FURTHER VIEW OF STEWART

The rejection of claims 9 and 12 under 35 U.S.C. §103(a) as allegedly obvious in light of Hein et al. in view of Hurwitz et al. and Rakowitz-Szulczynska et al., and in further view of Stewart et al. (USPN 6,087,452) was maintained. Applicants traverse in light of the amended claims and respectfully request that the rejection be withdrawn.

Claims 9 and 12 are also drawn to methods for detecting ligand internalization using epitope tags. Since these claims are ultimately dependent from claim 1, the methods also include the step of dissociating the reporter from non-internalized ligand bound to the cell surface and removing dissociated reporter from the surface of said cell while the non-internalized ligand remains bound to the cell surface. As noted above, neither Hein nor Hurwitz nor Rakowitz-Szulczynska teach or describe methods in which the dissociated reporter, but not the ligand, is removed from the cell surface. Stewart, which describes the use of polyhistidine/protein A for attachment of antibodies to another compound, does not remedy this deficit. Since the cited references, either alone or in

combination, do not teach all of the limitations of the claimed invention, the first criteria for *prima facie* obviousness has not been met. Applicants respectfully request that the rejection be withdrawn.

The Election/Restriction Requirement.

Claims 73-76 are directed toward the elected species of "Epitope Tag"

Claims 73-76 were withdrawn by the Examiner as allegedly directed to an invention that is independent or distinct from that elected in response to the restriction requirements mailed March 9, 2004 and June 30, 2004. Applicants traverse.

Claims 73-76 are drawn to methods for detecting ligand internalization employing polyhistidine (His) tags and metal chelation bonds. Applicants note that His tags were elected as the species of epitope tag for initial consideration in response to the restriction requirement mailed June 30, 2004. His tags are one of the most widely used epitope tags in the art, and are known for their affinity for metal ions and the subsequent ease in isolation using simple metal chelating resins. One of skill in the art would be recognize that the use of His tags typically involves an interaction between the metal ion and the imidazole ring of the histidine residue, i.e., via a metal chelation bond. Applicants note that the metal chelating properties of His tags are referred to in reference U (Dietrich et al) cited in Form 892 accompanying the Office Action mailed November 5, 2004. Descriptions of metal chelation with respect to His tags are also provided throughout the specification (see, for example, paragraphs [0096], [0099], and [0111], as well as the Examples). Thus, examination of claims encompassing the "His tag" embodiment of epitope tags would naturally include consideration of non-covalent bonding between the His tag and ligand via a metal chelation bond.

Applicants submit that claims 73-76 are not drawn to a different invention than what was elected for prosecution, and respectfully request that these claims be considered with the currently pending claims.

Additional Withdrawn Claims

Applicants note that claims 4, 80, 82, 90, and 91 are also deemed withdrawn by the Examiner. Should the remaining claims be found allowable, Applicants would be willing to cancel the remaining withdrawn claims without prejudice in order to expedite prosecution (and expressly reserving the right to file one or more continuing applications containing these cancelled claims).

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 337-7871 to schedule an interview.

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Respectfully submitted,

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Attachments:

1) A facsimile cover sheet;
2) A petition to extend the period of response for 1 months;
3) A transmittal sheet; and
4) A fee transmittal sheet.

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